

EPIDEMIC INFLUENZA*

THOMAS FRANCIS, JR.

Professor of Bacteriology, New York University College of Medicine

IN 1933, Smith, Andrewes and Laidlaw¹ announced that they had isolated from the nasal washings of influenza patients a virus which was pathogenic for ferrets by the intranasal route. The following year this observation was confirmed in our laboratory where strains of the same virus were recovered from epidemics in Puerto Rico,² the United States³ and Alaska.⁴ At the same time it was found that mice were also susceptible to the virus infection when anesthetized and inoculated intranasally.^{2, 5} Since then, the virus has been clearly established as the causative agent of epidemic influenza by the application of experimental methods to the study of individual cases in different epidemics.

THE DIAGNOSIS OF EPIDEMIC INFLUENZA

The laboratory diagnosis of epidemic influenza has employed essentially two approaches. The first, consisting of the isolation and identification of virus from the patient, is perhaps the most conclusive but also the most tedious and expensive. Commonly, the nasal washings of the patient are passed to ferrets and subsequent transfer of the virus is made to mice, where it can be satisfactorily identified by serological means. One can, however, allow the inoculated ferret to recover. In this case the presence of virus in throat washings is demonstrated by the appearance of antibodies to the virus in the animal's serum or in its capacity subsequently to resist active infection with known virus. Either method yields valid evidence of the presence of virus when positive; negative results are somewhat less significant.

The second approach makes use of the fact first demonstrated by Francis and Magill³ that infection of human individuals by the virus of epidemic influenza calls forth a sharp rise of antibodies in the convalescent serum. While it is known that antibodies are detectable in a large proportion of normal sera, by comparing serum taken from the patient

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during the acute phase of illness with that taken after recovery, the increase in titer can be measured. Two techniques are available: (1) the determination of the smallest amount of serum capable of protecting mice against fatal infection with a constant amount of virus, thus measuring the titer of neutralizing antibodies; (2) the determination of the smallest amount of serum which fixes complement in the presence of a constant amount of virus antigen prepared from infected mouse lungs or tissue culture medium.

Efforts have been made to gain knowledge not only concerning the frequency of virus infection in typical cases but to study the marginal cases as well, hoping in this manner to map the boundaries of the clinical picture. These observations have also served, reciprocally, to establish the value of the laboratory procedures for practical clinical purposes.

In order to demonstrate the frequency with which influenza virus can be identified in epidemic influenza patients, it will be well to summarize the experiences of various investigators in the winters of 1936-37 and 1938-39. Together with Magill, Rickard and Beck,⁶ at the laboratories of the International Health Division, during the epidemic period from December 1936 to March 1937, material for study was obtained from 100 patients in whom a final diagnosis of epidemic influenza was made. Throat washings from 64 of them were tested by ferret inoculation and in 52, or 81 per cent, the presence of virus was demonstrated. From 23 of the washings, strains of virus were actually established in mice. In England, Stuart-Harris, Andrewes and Smith⁷ similarly reported 75 per cent successful tests for virus from 40 typical cases although the number of strains transferred to mice was low. Moreover, in numerous other laboratories throughout the United States, Europe and the Far East, additional strains of the virus were recovered. Thus, from an epidemic of moderately severe influenza, pandemic in its distribution, the presence of the virus was demonstrable with relative ease in a high proportion of the patients attacked.

The results of 1938-39 offer an interesting contrast. The disease was not prominent in the general population but appeared more in the form of institutional outbreaks. Moreover, the clinical attacks were quite mild. Stuart-Harris, Smith and Andrewes⁸ reported the recognition of influenza virus in only 7 of 59 throat washings obtained in 12 institutions. All of the positive results were had in late February or March. The strains of virus were of low pathogenicity for ferrets and were

adapted to mice with difficulty. Horsfall, Hahn and Rickard⁹ studied 4 localized epidemics in January to March 1939. Throat washings from 65 cases were subjected to repeated ferret passage. Of these, 14 gave rise to antibodies in the ferret and 9 strains were adapted to mice. Our investigations in the same period apply more to the general population. No epidemic was recognizable. Throat washings were obtained from 28 selected patients among the nursing staff and patients on the wards of the Third Medical Division of Bellevue Hospital. In 3 instances the presence of influenza virus was shown by the development of antibodies in the inoculated ferret.¹⁰ No strains were established in mice. In Australia, Burnet and Lush¹¹ reported the isolation of mild strains of virus in July 1939.

Hence, in the early months of 1939 when mild isolated outbreaks were observed in different parts of the world the virus was less readily isolated and the incidence of detection was approximately one-third that noted in the more severe outbreak of 1936-37. The uniformity with which virus can be recovered appears, therefore, to be related to the pathogenicity of the prevalent strains of virus and it becomes obvious that this procedure is unsuited to the diagnosis of a large number of individual cases.

Serological studies were also carried out in relatively large numbers of patients. Their value was established by a consideration of the results of the neutralization or complement fixation tests in relation to virus identification. Thus, in 1937 titrations of neutralizing antibody were made with acute and convalescent sera of 41 patients from whose throats virus had been recovered.⁶ In each instance a sharp rise in the titer of the convalescent serum was observed. The average titer in the early days of illness was 22 while in convalescence it reached the high level of 235. The uniformity of response indicated that the virus infection and the increase in titer were associated phenomena. When comparable antibody responses were observed in the sera of patients from whom either virus was not recovered or throat washings were not collected, it was reasonable to conclude that the rise of antibodies was due, nevertheless, to infection by the same virus. Conversely, those cases of various clinical types, from whom virus could not be recovered and whose convalescent titer was essentially unchanged from the normal level were considered to have suffered from infections of different etiology. The results of the neutralization tests were verified by Stuart-Harris, An-

drewes and Smith⁷ in a study of sera from 23 patients in the English epidemic of that year.

Following a procedure similar to that described by Fairbrother and Hoyle¹² the same sera were then tested in the complement fixation reaction.⁶ Results, strikingly comparable with those of the neutralization tests, were obtained. An average rise in titer of tenfold to twentyfold was recorded in sera from the groups of patients which had yielded the positive neutralization tests. The groups of sera which yielded negative results by the neutralization test revealed no significant change in the complement fixation titers.

Hoyle and Fairbrother¹³ had also noted the rise in complement-fixing antibodies during convalescence in 8 patients and observed further that the titers of convalescent patients were, in general, considerably higher than those of the general population tested immediately prior to the epidemic.

In the mild epidemic of 1938-39, when the incidence of virus detection was low, the serological tests maintained their efficiency in identifying cases of the disease. Stuart-Harris, Smith and Andrewes⁸ were, by the neutralization test, able to demonstrate the occurrence of epidemic influenza in 4 institutions when virus was not isolated. At New York University virus¹⁰ was demonstrated in only 3 of 28 patients. Acute and convalescent sera were obtained from 14 of the patients, however, and half of them showed the characteristic rise in neutralizing antibodies. The extensive studies of Horsfall, Hahn and Rickard⁹ during the same period are extremely noteworthy. While in only 21 per cent of throat washings tested was the presence of virus proven, neutralization tests with the sera of these patients revealed a diagnostic increase of antibodies in 93 per cent. But, strikingly, in only one of 83 patients with non-influenzal respiratory infections was a comparable mounting of the titer observed. This shows clearly the significance of the test in establishing the etiology of the disease in a large group of patients which otherwise would not have been identified. The value of the serological reactions has thus been tested in two epidemics of greatly different severity and extent. One, with a high incidence of infection in the general population, pandemic in distribution, demonstrated the causal relationship of virus infection and positive serological tests; the other, recognized primarily in institutions in this country and abroad, was caused by virus which produced a mild illness, and was of low pathogenicity

for animals. In this outbreak the significance of the serological tests was enhanced, for, while virus was isolated from only a minority of cases, the circulating antibody titers identified the individual case just as accurately as in the preceding epidemic.

The investigations have confirmed the accepted theory that influenza is an epidemic disease in which a high proportion of cases presents a great uniformity of symptoms. It has been demonstrated, however, that distinct variations may occur. Thus, in 1936-37 in a group of contacts who exhibited no signs or symptoms of the disease, serological studies revealed that approximately 25 per cent had actually undergone virus infection. A similar incidence is recorded by Horsfall, Hahn and Rickard⁹ in 1939. The importance of clinically undetected cases as agents of dissemination becomes apparent.

Certain information has been gained concerning the so-called relapses which some authors have considered a characteristic of epidemic influenza. There is ample evidence that serious pulmonary disease may follow what appears to be simple influenza. The most common is a mild bronchitis or bronchiolitis which develops slowly as the acute illness subsides. The usual story of the relapse is, however, that about the time of recovery the patient has a recurrence of fever and may then develop pulmonary disease. Numerous observers have considered such episodes to be secondary infections and the evidence of the virus studies clearly supports this conclusion. In 1936-37 we had the opportunity of studying material from 7 such patients.⁶ They gave histories of moderate illness for 6 to 8 days and a sudden exacerbation of symptoms and fever prior to their admission to hospital. Bacteriological diagnoses of atypical pneumococcus pneumonia had been made in 2, acute pneumococcal bronchitis in 1, hemolytic streptococcal tracheitis in 1; 3 were simply called relapses of influenza. At the time they were first observed in the hospital, the serological tests revealed high antibody titers quite characteristic of the patient convalescent from virus infection. Virus was not detected in the 3 throat washings tested. It is evident, therefore, that the relapses were bacterial infections developing in convalescence from the virus disease. Stuart-Harris⁷ has recorded relapses due to pulmonary disease in 3 patients and in 5 others due to acute hemolytic streptococcal tonsillitis. Cases of this general character illustrate clearly the lack of reason in considering the relapse a recrudescence of the primary virus infection. They are obviously caused by secondary bacterial invaders.

The same comment applies to the post-influenzal pneumonias occurring within a short interval after recovery. On the other hand, the British group⁷ have reported the isolation of virus from 3 patients dying of pneumonia within 5 days of onset of influenza. In all of them cultures of the lungs revealed heavy growth of *Staphylococcus aureus* as well. We also⁶ recovered virus on the second day of the disease from a patient with a simultaneous bacterial infection due to *Pneumococcus* Type III. This indicates that the possibility of severe respiratory disease beginning synchronously with the onset of the virus infection is an attribute of the bacterial agent. It is noteworthy that through the epidemics discussed, bacteriological studies have not disclosed a preponderance of a particular organism. In fact, the great majority of cultures have resembled the normal nasopharyngeal flora. It seems likely that the differences in mortality in different epidemics depend upon the nature of the bacteria prevalent at the time and that any of the common respiratory pathogens may be responsible for the serious complications.

Recognition of the average cases in the course of an epidemic is aided by their relative uniformity. A sudden onset is the rule, with fever and constitutional symptoms in the absence of prominent respiratory complaints such as the sore throat of tonsillitis or the nasal discharge of the common cold. The course is short and convalescence is relatively prompt except for residual fatigue. Either leukopenia or the absence of leukocytosis in the early days is a significant observation. Nevertheless, a diagnosis of epidemic influenza in the individual patient, considered out of relation to an epidemic, can not be made purely on the basis of clinical observation. In fact, the readiness with which a diagnosis of influenza is made under these conditions is inversely proportionate to the physician's diagnostic accuracy. Because of this, the early cases of an epidemic in a general population are usually recognized in retrospect. Moreover, epidemics and outbreaks of diseases as remote as yellow fever and lymphocytic choriomeningitis have been so diagnosed. These facts illustrate the relative non-specificity of the symptom complex.

Just as the confirmation of clinical diagnosis in so many illnesses depends upon the use of laboratory aids, so is it in epidemic influenza. Only with increasing efforts to establish the diagnosis etiologically will the clinical problem be solved. One can point out certain differentials which should be made and maintained. Epidemic influenza applies to

the disease in its abrupt epidemic form; there is no evidence to date that sporadic cases of the virus disease occur except in relation to an epidemic period. It is essentially a febrile, prostrating, brief disease; it is not the afebrile common cold with profuse discharge but with few constitutional symptoms; nor is it the purulent complication of the common cold. In acute pharyngitis, tonsillitis or sinusitis caused by the hemolytic streptococcus, pneumococcus, staphylococcus or Pfeiffer's bacillus the organisms can be identified, if the effort is made; these are not epidemic influenza. While a certain number of patients with epidemic influenza may have gastrointestinal disturbances, as is the case with numerous acute infections, there is little justification for the term, intestinal flu; etiological investigations have usually revealed food or water borne infection in outbreaks so designated.

There is in addition that group of irregularly distributed, low-grade respiratory infections of the winter season which the British writers have called febrile catarrh.⁷ They bear little close resemblance to typical epidemic influenza but more probably represent bacterial infections of low pathogenicity and transmissibility. The use of the term, febrile catarrh, may well be a suitable one provided there is at the same time an admission that it is merely descriptive. No single etiology for these cases has been recognized.

Mention must also be made of certain epidemics bearing a close resemblance clinically and epidemiologically to those caused by the virus of epidemic influenza but in which all reported studies have failed to implicate that virus. One such epidemic was widespread throughout the entire United States early in 1936,⁴ another this year. These outbreaks have recently been shown to be caused by a new type of virus¹⁴ clearly different from that previously recognized. The entire field must, therefore, be reinvestigated in this light.

I have tried to show how the investigations to date have established the virus etiology of epidemic influenza and to summarize representative results from which that conclusion is drawn. Through the methods outlined a definitive picture of the disease and its variations is taking form. In this instance, as so often before, the establishment of diagnosis on the basis of etiology is serving to bring order in a field of infection which has been the source of marked clinical confusion.

To many minds the term, epidemic influenza, connotes only the devastating disease of the autumn of 1918. A survey of the history of

influenza reveals on the contrary that the world-wide scourge of 1918 looms from the pages of history as an episode without counterpart in the centuries through which physicians have recorded the characteristics of its not infrequent visitations. It was not unique in its spread throughout the world; it was not unique in the proportion of the population attacked or in the fact that it was looked upon as something entirely new to that generation of physicians. The rate of dissemination, the frequency of severe pneumonias which accompanied it and the mortality rate were, however, unprecedented.

It is well to recall that the autumnal outbreak of that year did not arrive unheralded. In the winter of 1915-16 an extensive epidemic took place. The influenza of the spring and summer of 1918 differed in no essential feature from that of recent years. Furthermore, practically all observers refer to the uncomplicated cases in the autumnal wave as 3-day fevers and it should be remembered that they constituted 80 to 90 per cent of the total in 1918. In other accepted pandemics the percentage of complications was extremely low, even though the incidence of disease was high. Thus, the term, pandemic, is not synonymous with high mortality.

It is my firm belief that the epidemics of varying extent which occur from year to year are the typical disease and that an episode such as that of the fall of 1918 represents a bizarre occurrence due probably to a simultaneous visitation of virulent influenza virus and a widespread dissemination of highly invasive bacteria of various species. Hence, the results of recent investigations, seeking insight into the accepted and debated opinions, appear applicable to the problem of influenza as a whole.

MEASURES TOWARD PROPHYLAXIS OR THERAPY

Early in the course of virus studies attention was attracted by the fact that when large doses of active influenza virus were given to experimental animals by routes other than the intranasal, characteristic infection did not occur. Nevertheless, animals developed antibodies and became immune to virus given by the usual mode of inoculation. Furthermore, Shope¹⁵ demonstrated with swine influenza virus that, in ferrets, subcutaneous vaccination elicited an excellent antibody response and that when such animals were subsequently infected intranasally, they were protected against pulmonary invasion even though a febrile

reaction and some nasal signs developed. These results have been amply confirmed with human strains. Furthermore, it has been practically impossible to recover virus from animals so treated, showing that vaccination increases the capacity to dispose of the infectious agent. These observations suggested that a similar series of events might be induced in man. In 1935 we conducted experiments to test this hypothesis.¹⁶ It was found that the subcutaneous injection of relatively large amounts of active virus did not induce clinical infection in human subjects but that a sharp rise in circulating antibodies occurred. Since a rise in antibodies occurs as a result of infection and is associated with the immunity of convalescence, it seemed probable that the rise which followed vaccination also indicated the development of an increased resistance.

In this country an evaluation of subcutaneous vaccination of active virus as a measure protective against the natural disease in man has been attempted by Stokes and his associates^{17, 18} and by Siegel and Muckenfuss.¹⁹ The results have not justified a straightforward conclusion. In 1936 the figures obtained by Stokes and others, suggested a beneficial effect but subsequent studies have not been easily interpreted. Siegel and Muckenfuss in 1938-39 failed with the material they used to observe a satisfactory antibody response and, as would be expected, no statistically significant protection was noted. Thus, the procedure has not proven itself and the results so far have not been conclusive enough to permit any verdict. Under proper conditions, involving the use of a sufficiently good virus preparation to function as a proper antigen, and the coincidence of a well established outbreak of epidemic influenza in the test community, evidence will be gained, but not otherwise.

In England a vaccine of formolized inactive virus has been shown by Andrewes and Smith²⁰ to give rise to immunity in mice inoculated intraperitoneally and also to induce the formation of antibodies in human subjects. Nevertheless, the immunity has not been as firm as that produced by active virus. The results of its application to man have yielded no indication of protection against the natural disease.

More recently, Horsfall and Lennette²¹ have reported the enhancement of immunity to influenza, in ferrets vaccinated with mixtures of inactivated influenza and canine distemper viruses. This interesting phenomenon is being intensively studied.

Despite the lack of information there has been a lurking suspicion that the subcutaneous injection of active virus would not be entirely

satisfactory under the most careful conditions. After all, it is clear that ferrets do not develop a complete immunity, and even in mice the resistance acquired as a result of subcutaneous vaccination is never as great as that which follows intraperitoneal immunization. Because of this we have been led to further consideration of the use of the nasal route for prophylactic procedures. The fact that subclinical infection in epidemic periods is common and the fact that the mere presence of antibodies is not synonymous with immunity have been well established. It seemed not unlikely that agents active in the nose might be important factors in determining clinical response since this is the primary point of attack of influenza virus. Together with Stuart-Harris²² it was demonstrated that ferrets recovering from virus infection developed a new type of transitional-squamous epithelium which was resistant not only to virus but to severe physico-chemical injury with zinc sulphate ionization as well. Unfortunately, the change was not a permanent one but the respiratory mucous membrane was so conditioned that repair following reinfection was markedly accelerated. The possibility exists that changes of this sort bear some relation to the variations in resistance of different individuals and that these modifications could be influenced and maintained by nasal vaccination.

In addition, studies in our laboratory²³ and that of Burnet²⁴ have revealed that the nasal secretions of human subjects may contain a substance capable of inactivating relatively large amounts of the virus of epidemic influenza. A wide variation in the inactivating capacity is seen in the secretions at different ages or in different individuals of the same age. Since both the cellular factor and this serological factor are resident in the nose where the virus initiates infection, it may be that the local introduction of virus antigen by stimulating these mechanisms might produce more benefit than would accrue from simply increasing antibodies in the general circulation. Experiments to investigate these possibilities are being carried on at the present time. It has been found that as much as 10,000 mouse-lethal doses of virus cultivated in tissue culture medium can be given intranasally to human subjects without producing infection.²⁵ To what extent immunity develops has not yet been ascertained. It may be that only those whose nasal secretions are devoid of virus-inactivating substances need be subjected to immunizing procedures.

While it is apparent from this recital that prophylaxis against the

virus of epidemic influenza in man is in the experimental stage, the outlook on theoretical grounds appears quite promising. The procedures which are being carried out have a firm and clear-cut foundation in the results of animal experimentation. One difficulty which I do not propose to discuss at present is that strains of the virus may differ. If, however, an effective method of producing immunity against any one strain is established, the rest will follow. As previously stated, one of the chief obstacles to proper evaluation is the lack of coöperation on the part of the disease itself, in not presenting itself in the desired spot at the desired time.

Thus, while attempts to devise a satisfactory prophylactic procedure are being carried out, other efforts are also going on which may have a bearing on clinical therapy of epidemic influenza. It has been shown repeatedly that the injection of potent immune serum intraperitoneally into mice will give excellent passive immunity. More recently, Smorodintseff,²⁶ and Stokes, Henle and Shaw²⁷ have reported the fact that when the serum is given by the intranasal route even as late as 24 to 48 hours after infection of mice, fatal outcome may be prevented. These indications are suggestive. Certain clinical observations of 1918 also contain hints that convalescent serum may be of benefit.

On the other hand, chemotherapeutic agents have given no indication up to the moment of exerting any curative or prophylactic effect upon the virus disease in experimental animals. Since, however, the evidence points to the fact that the fatalities in epidemic influenza are to a great extent dependent upon bacterial complications, I believe that chemical therapy will be of tremendous value in controlling mortality.

In the presence of a highly virulent virus which of itself would produce a great incidence of pneumonia the outlook would be more problematic. Up to the present, rest, isolation and respiratory comfort have not been supplanted. Probably the most valuable factor in the control of epidemic influenza is increased emphasis on respiratory hygiene, if any such thing exists.

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